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PEPTIDE-INDUCED EMESIS IN DOGS: POSSIBLE RELEVANCE TO RADIATION-INDUCED EMESIS

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NOTICES

This final report was submitted by New York State Department of Health, Albany, New York, under contract F33615-78-D-0617, jo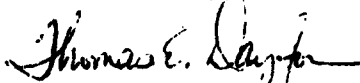b order 7757-05-49, with the USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas. Captain Thomas E. Dayton (USAFSAM/RZW) was the Laboratory Project Scientist-in-Charge.

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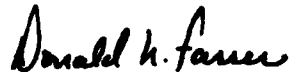
The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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Results of earlier investigators indicate that radioemesis is mediated by some humoral agent(s). Peptides are likely candidates since they exert a number of biological effects and are released from storage sites by various stimuli, including radiation. Peptides at various concentrations were injected singly intravenously into conscious dogs, and the dog's emetic response was observed. Of the peptides tested, neurotensin, angiotensin II, vasopressin, oxytocin, and TRH produced consistent emetic responses.

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20. ABSTRACT (Continued)

Inhibition of drug-induced emesis was studied using both centrally (chlorpromazine) and peripherally (domperidone) acting dopamine antagonists. Results indicate inhibition by chlorpromazine, which crosses the blood brain barrier, but only partial blockade by domperidone, which does not cross the blood brain barrier.

Preliminary studies were conducted attempting to characterize types of receptors on area postrema neurons. Single-cell recordings from these neurons, challenged by iontophoretic administration of various neurotransmitters, show stimulation by glutamic acid and serotonin and inhibition by norepinephrine.
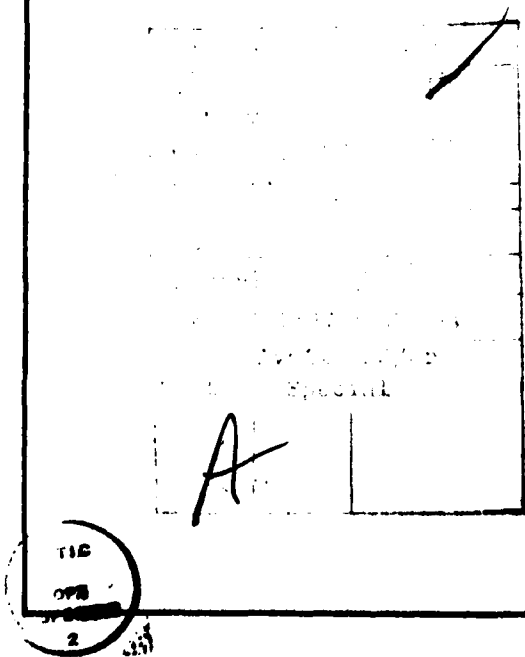
PEPTIDE-INDUCED EMESIS IN DOGS:
POSSIBLE RELEVANCE TO RADIATION-INDUCED EMESIS

INTRODUCTION

Emesis is frequently present in a variety of gastrointestinal illnesses resulting from either infection or local irritation causes. In these circumstances emesis may have value to the organism since it clears the stomach and upper small bowel of contaminated food. Emesis, however, is also an unpleasant side effect of drug therapy, various types of repetitive motion, and exposure to ionizing radiation. In these circumstances it is not clear what the benefit is to the organism. Because emesis can be very debilitating as well as unpleasant, it is important to understand the normal physiology and pharmacology of this process, with the aim of developing a pharmacologic prophylaxis.

Most of our present knowledge of the central nervous mechanisms controlling emesis comes from the work of S. C. Wang and his students (2, 3, 4). In 1947 Borison and Wang (2) demonstrated that they could elicit emesis by electrical stimulation of the lower brain stem, localized to a region corresponding to the solitary nucleus and the dorsolateral border of the lateral reticular formation. Further studies (summarized by Borison and Wang (3) demonstrated that the motor act of emesis could be elicited through two separate neuronal pathways. Local gastrointestinal irritation, such as can be experimentally induced by intragastric administration of copper sulfate solutions, excites afferent neurons which ascend to the motor emetic center via the vagus nerve to elicit vomiting. Drug-induced emesis, as typified by apomorphine-induced emesis, is abolished by ablation of the area postrema. The area postrema, located at the floor of the fourth ventricle, is one of the circumventricular organs and is outside of the blood brain barrier. Neurons in the area postrema are therefore exposed to circulating substances. Borison and Wang (3) coined the term, chemoreceptive trigger zone (CTZ), for the area postrema (or portion thereof) responsible for all but the motor response of humorally induced emesis. They proposed that the CTZ contains neurons responsive to emetic agents, and that excitation of these neurons causes excitation of the motor-emetic center. While several other functions have been ascribed to the area postrema, there is no clearly documented function other than its role in emesis (cf. Borison (4)).

Radiation-induced emesis is abolished by area-postrema ablation (6, 9). Further, radioemesis does not require head irradiation and is in fact most common in man with focal abdominal irradiation (12). Chinn and Wang (9) reported that shielding of the area postrema did not prevent radiation-induced emesis. These results indicate that radioemesis is mediated by a humoral agent, presumably released by radiation from a peripheral site, which excites area-postrema neurons. The identity of this substance or substances is unknown.

The present experiments were begun as part of a multidisciplinary program to identify the humoral agent(s) responsible for radioemesis. Because of a rapid increase in knowledge of biological effects of small peptides and the known findings that these peptides may be released from various storage sites by a variety of stimuli, we have attempted to test whether or not known small

1

peptides may be mediators of radioemesis. In this portion of the project, we have studied the results of intravenous injection of peptides in order to determine which are possible mediators of radioemesis. In addition we have performed initial studies on chlorpromazine and domperidone, two antiemetic agents, to determine their effectiveness as blockers of peptide-induced emesis.

Necessary experiments investigating radiation-induced biochemical changes in the blood were concurrently performed by Magro (18).

METHODS

Peptide Injections in Conscious Dogs

Conditioned random-source dogs (10 to 15 kg) were obtained from Biomed Associates, Inc., Friedensburg, Pa., and maintained on dog chow. Peptides, dissolved in physiological saline, were injected IV in restrained conscious dogs no more frequently than on alternate days. The following drugs were used: apomorphine hydrochloride, Sigma; thyrotropin releasing hormone (TRH), Sigma; 8-lys-vasopressin (LVP), Calbiochem; oxytocin synthetic, Calbiochem; gastrin (porcine), Sigma; substance P, Sigma; vasoactive intestinal peptide (VIP), Sigma; angiotensin II, Sigma; neurotensin, Sigma; mast cell preparation, Magro; cholecystokinin (pancreozymin), Sigma; compound 48/80, Sigma; bradykinin triacetate, Sigma; methionine enkephalin (synthetic), Sigma; L-carnosine (β-alanyl-L-histidine), Sigma; somatostatin (inhibiting factor for growth-hormone release), Sigma; prostaglandin E, Magro. Following injection the dogs were put back in their cages and observed for 20 minutes with attention being paid particularly to presence or absence of emesis; all other systemic effects of the peptides injections were also noted. Antiemetics were injected IM 15 minutes before IV injection of peptides. Substances used were chlorpromazine hydrochloride, Sigma, and domperidone, Janssen Pharmaceutica.

Single Unit Recording from Area Postrema

Single unit studies were performed on 8 random-source dogs (Biomed Associates, Inc., Friedensburg, Pa.) and 25 colony-bred cats (Cornell Univ. School of Veterinary Medicine). Cats were initially anesthetized with 100 mg Ketaset intraperitoneally, while dogs were initially anesthetized with 25 mg/kg Surital IV. Arterial and venous cannula were inserted, as well as an endotrachial tube and rectal thermometer. Animals were initially given α-chloralose IV (65 mg/kg for cats and 100 mg/kg for dogs) for prolonged anesthesia. Supplemental doses (20 mg/kg) were given as needed. Respiratory rate, heart rate, and blood pressure were used as indicators of the necessity for additional anesthetic. Temperature was maintained by a thermostatically controlled heating pad. Animals were mounted in a Kopf stereotaxic frame with their heads angled steeply down to facilitate surgical exposure of the area postrema. An incision was made over the fourth ventricle area, with removal by suction of a small portion of the cerebellum in order to visualize the full extent of the area postrema. The exposed brain stem was kept covered with mineral oil to prevent drying. A pneumothorax was performed bilaterally to reduce brain-stem pulsations, and the animals were respirated with a Bird small-animal respirator. Neurons were recorded with the center barrel of a seven-barrelled micropipette filled with

2

2.5M NaCl. The remaining six barrels contained the transmitters to be studied, and these initial experiments were glutamic acid (1M, pH 7-8), aspartic acid (1M, pH 7-8), acetylcholine chloride (1M, pH 3-4), norepinephrine (0.5M, pH 3-4), 5-hydroxytryptamine (0.1M, pH 3-4), and dopamine (0.5M, pH 3-4). All recording techniques were as previously described (5). Following experimentation the animals were euthanized with 100 ml of 3M potassium chloride given IV.

RESULTS

Peptide Injections in Conscious Dogs

Figure 1 illustrates the emesis and pharmacologic antagonism of emesis induced by injection of apomorphine. At doses of 0.01 mg/kg and higher, apomorphine regularly induced emesis with a delay of 1 minute or less. Chlorpromazine at 1.5 mg/kg, a classical dopamine-receptor antagonist, blocked the apomorphine-induced emesis, as did domperidone at 1 mg/kg. Domperidone is a dopamine-receptor antagonist but does not readily cross the blood-brain barrier (15). Since apomorphine is assumed to act at dopamine receptors on area-postrema neurons, blockade of apomorphine emesis by these two drugs is expected.

A dose-dependent emesis was observed with injection of several peptides. Figure 2 shows results with neurotensin. Emesis was found consistently at doses of .02 mg/kg and greater. As with apomorphine, neurotensin emesis was very brief in latency and was not associated with other obvious systemic signs. Neurotensin emesis was blocked by chlorpromazine (1.5 mg/kg). The effects of domperidone to date have been somewhat inconsistent, in that it appeared to block high doses of neurotensin in several animals, although it did not block lower doses in others.

Figure 3 shows results of intravenous injection of angiotensin II on the emetic response. At concentrations higher than 0.02 mg/kg, angiotensin II consistently produced emesis that was of short latency and was not accompanied by other obvious systemic effects. Very preliminary experiments with domperidone (1 mg/kg) suggested at least a partial blockade of the angiotensin-induced emesis.

Figure 4 shows the emetic reflexes induced by injection of 6 other peptides, although these peptides were not studied as extensively as neurotensin and angiotensin II. Thyrotropin-releasing hormone was emetic in one dog at 0.5 mg/kg. Oxytocin and TRH produced emesis with few other obvious systemic effects. Vasopressin also induced emesis, accompanied by micturition. Gastrin, substance P, and VIP all appeared to show a dose-dependent emesis, but all were accompanied by indications of gastrointestinal activation, including retching, defecation, and often an obvious increase in peristalsis.

Several other peptides produced no emesis (Table 1). In addition, histamine did not produce emesis, although intravenous injection was severely debilitating to the animal, producing unsteady gait, micturition, and defecation.

3

TABLE I. PEPTIDES WITH NO EMETIC RESPONSE

Drug	Drug concentration tested (mg/kg)
Mast cell preparation	0.020-0.026
Cholecystokinin	0.055
Secretin	0.058-0.061
Compound 48/80	0.058-0.061
Bradykinin triacetate	0.058-0.061
Methionine enkephalin	0.055-0.058
Carnosine	0.038-0.060
Somatostatin	0.030-0.048
Prostaglandin E_1	0.175

In this 9-month working period, a major part of the effort was devoted to developing techniques for recording, with multibarreled extracellular electrodes, from individual neurons in the area postrema and applying various neurotransmitters and antagonist substances onto such neurons by the techniques of iontophoresis. The study of this area was technically difficult, principally due to the small size of the neurons and the pulsations normally occurring in the brain stem due to nearby arteries. Although we have not yet studied the receptors for various neuropeptides in the area postrema, we have made major progress toward overcoming the technical difficulties and achieving stable and relatively long-term recordings in individual neurons in the area postrema. These experiments have utilized both dogs and cats, and to date no obvious differences have been seen in the properties of single units. We have perfected the surgical approaches to the area postrema and have learned to deal with the excessive bleeding which was a very serious problem in the initial experiments.

In the recordings we have made to date, we have found that neurons in the area postrema are either silent or have a very slow, relatively regular rate of spontaneous discharge. All neurons have been excited by glutamic and aspartic acids, resulting in a brief excitatory response. Most neurons have been excited by serotonin, but the response to serotonin differs dramatically in character to that of glutamic acid. Whereas the cells respond to glutamic acid at applications of 100 nanocoulombs or less, excitation by serotonin usually requires at least 1,000 nanocoulombs and often repetitive application of several pulses of 1,000 nanocoulombs. The excitatory response is slow at onset and very prolonged, frequently lasting for several minutes. Serotonin often has the effect of making a previously silent cell spontaneously active, and this has proved valuable for looking at the actions of transmitters that give inhibitory responses, such as norepinephrine. Norepinephrine has inhibited almost every neuron that we have studied. Most cells have not been responsive to acetylcholine.

No obvious differences have been observed in the responses, the spontaneous activity, or the sensitivity of neurons in different portions of the area postrema. This suggests the possibility that all neurons in the area postrema are involved in the emetic reflex. Considerable additional work must be done, however, to determine whether or not the CTZ is only a portion or all of the area postrema.
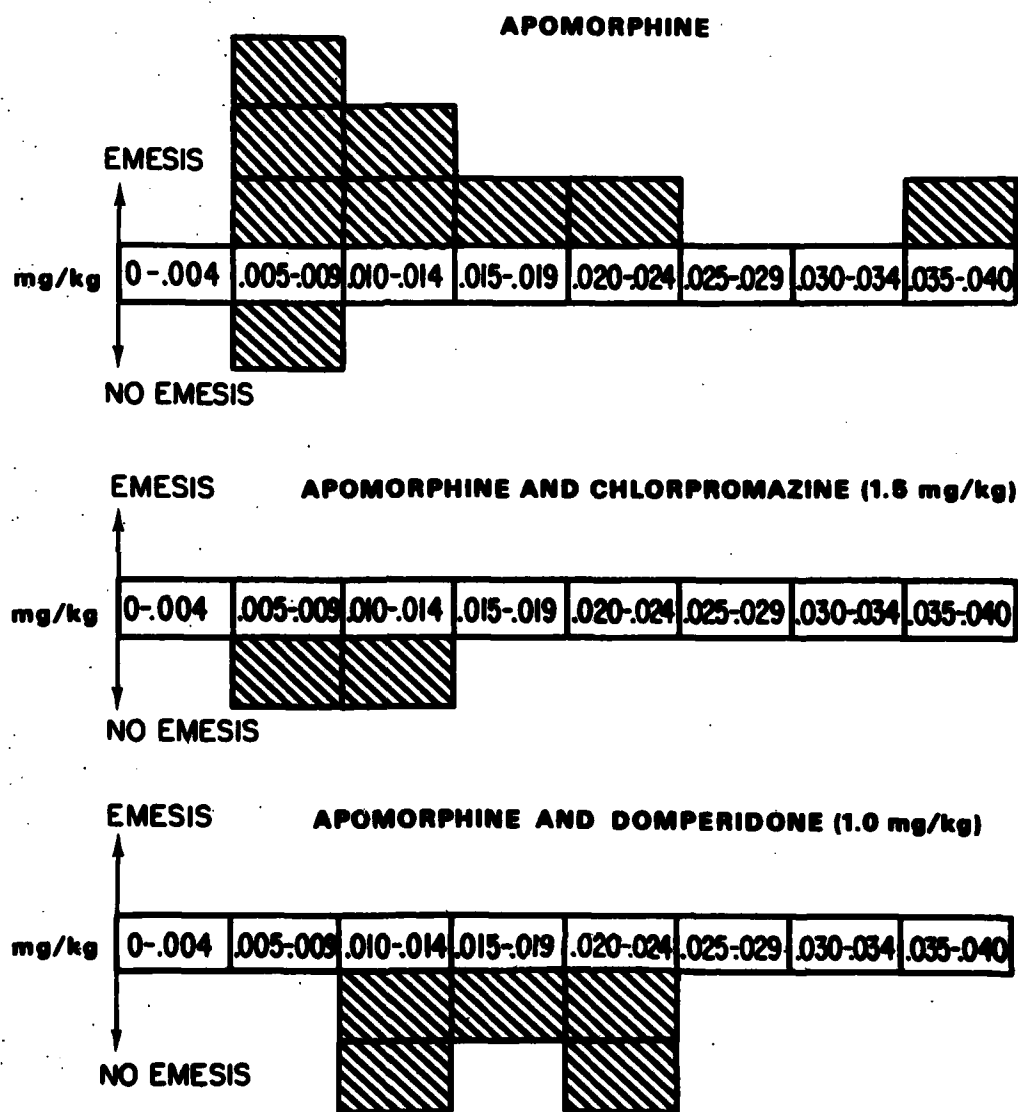
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Figure 1. Apomorphine-induced emesis in dogs at various concentrations and the effect of chlorpromazine and domperidone on the emetic response. Chlorpromazine and domperidone were administered IM 15 minutes prior to the IV injection of apomorphine.

Key: Each block = one trial.
     Blocks above concentration line = emesis.
     Blocks below concentration line = no emesis.

5

NEUROTENSIN

EMESIS

mg/kg | 0-.009 | .010-.014 | .015-.019 | .020-.024 | .025-.029 | .030-.034 | .035-.039 | .040-.044 | .045-.050

NO EMESIS

NEUROTENSIN AND CHLORPROMAZINE (1.5 mg/kg)

EMESIS

mg/kg | 0-.009 | .010-.014 | .015-.019 | .020-.024 | .025-.029 | .030-.034 | .035-.039 | .040-.044 | .045-.050

NO EMESIS

NEUROTENSIN AND DOMPERIDONE (1.0 mg/kg)

EMESIS

mg/kg | 0-.009 | .010-.014 | .015-.019 | .020-.024 | .025-.029 | .030-.034 | .035-.039 | .040-.044 | .045-.050
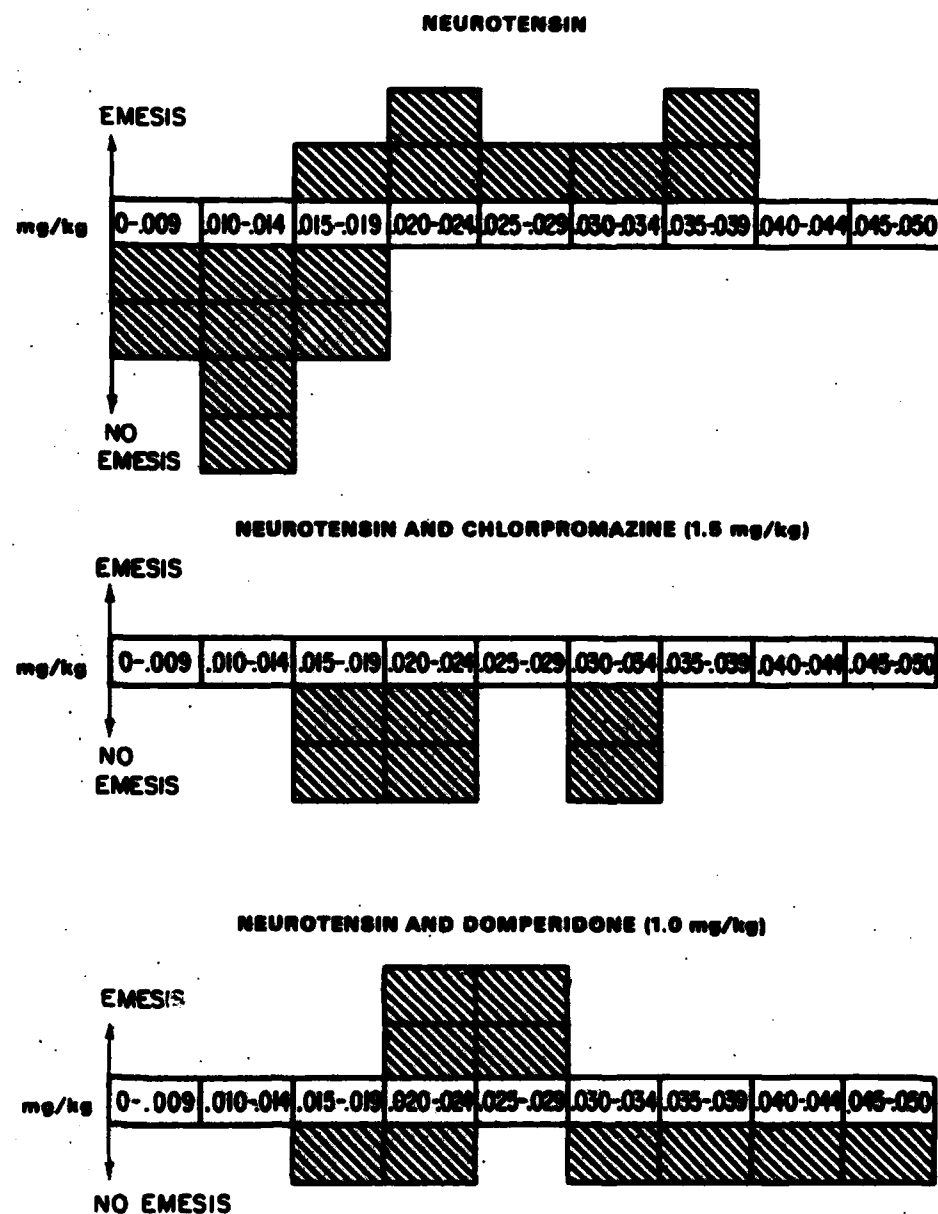
NO EMESIS

Figure 2. Neurotensin-induced emesis in dogs at various concentrations, and the effect of chlorpromazine and domperidone on the emetic response. Chlorpromazine and domperidone were administered IM 15 minutes prior to IV injection of neurotensin. (See Fig. 1 for key.)

6

ANGIOTENSIN II

EMESIS

mg/kg | 0-.009 | .010-.019 | .020-.029 | .030-.039 | .040-.049 | .050-.059 | .060-.070

NO EMESIS

ANGIOTENSIN II AND DOMPERIDONE (1.0 mg/kg)

EMESIS

mg/kg | 0-.009 | .010-.019 | .020-.029 | .030-.039 | .040-.049 | .050-.059 | .060-.070
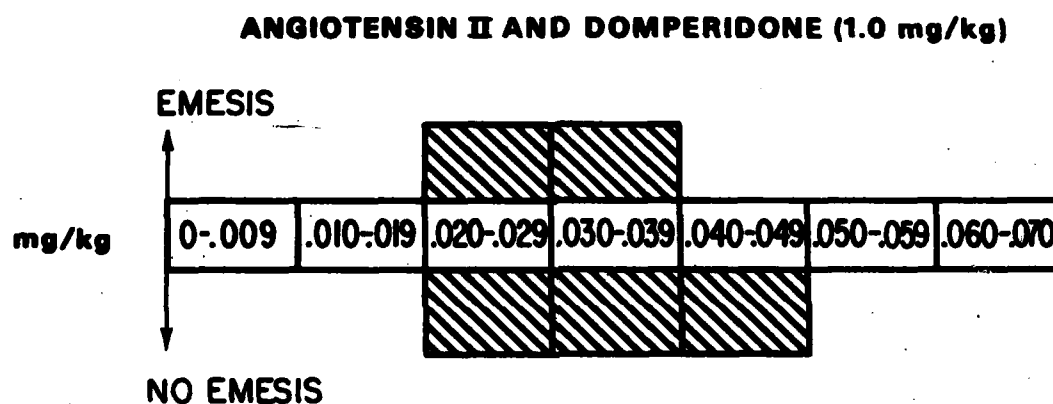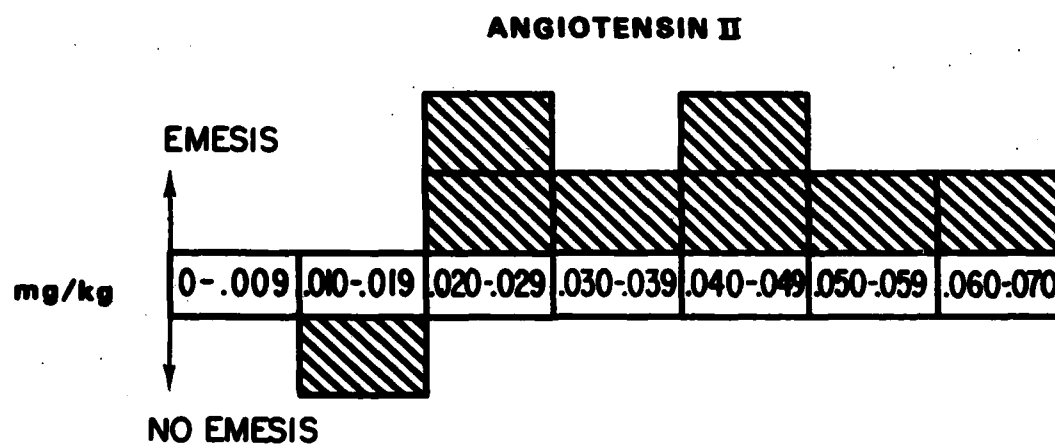
NO EMESIS

Figure 3. Angiotensin II-induced emesis in dogs and the effect of domperidone on the emetic response. Domperidone was administered IM 15 minutes prior to IV injection of angiotensin II. (See Fig. 1 for key.)
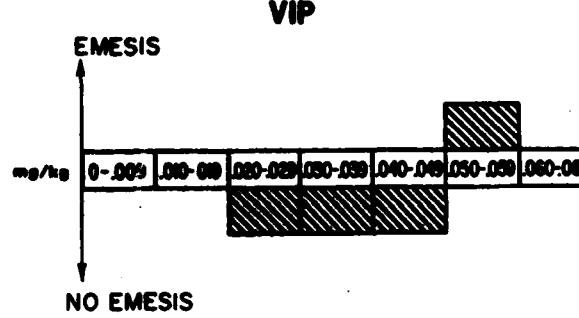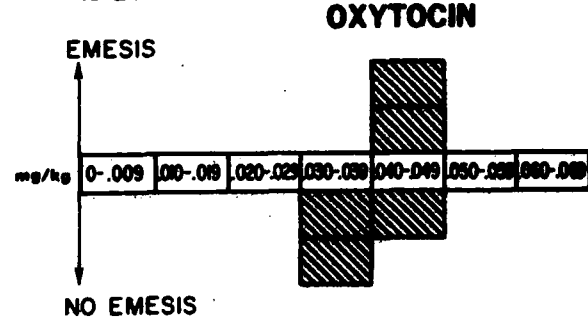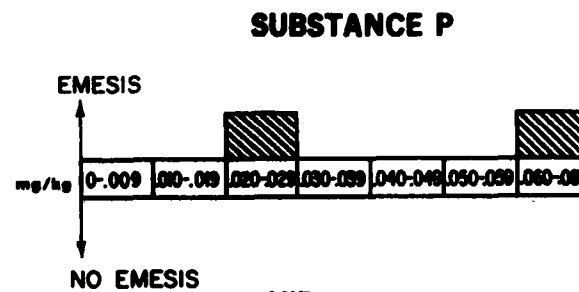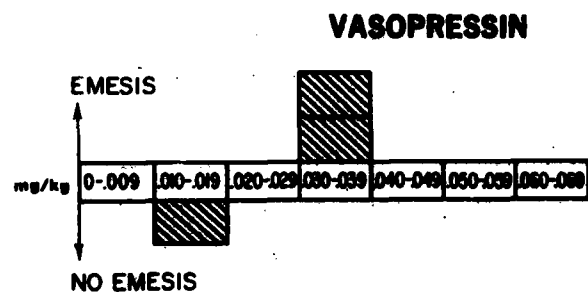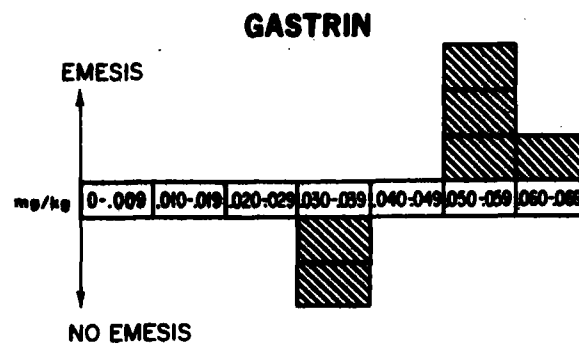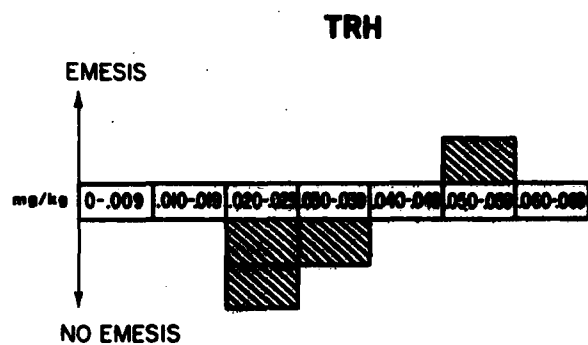
Figure 4. Emesis induced by various other peptides injected IV in restrained conscious dogs. (See Fig. 1 for key.)

DISCUSSION

These preliminary results indicate that several peptides are potent emetic agents; thus they are possible mediators of radiation-induced emesis. These results do not, of course, provide evidence for release of the peptides by ionizing radiation. They do, however, indicate specific peptides worthy of further study, especially neurotensin, angiotensin II, TRH, vasopressin, and oxytocin. All of these substances induced a short-latency emesis with few other obvious effects. The peptides which had no effect or produced emesis accompanied by other systemic effects are unlikely candidates, since the emesis induced by radiation in animals or man is not accompanied by a marked gastrointestinal activation. It is of interest that enkephalin (0.05 mg/kg) did not produce emesis, even though vomiting with narcotic agents is common in man, and emesis has been demonstrated in dogs with intraventricular injection of enkephalin (1). Possibly the concentration we used was too low for this effect to be seen.

Emesis due to a variety of agents and causes is depressed by dopamine- and histamine-receptor antagonists (11, 17). Radiation-induced emesis has been reported to be blocked by chlorpromazine (14, 19), perphenazine (12), penfluridol (16), and thiethylperazine (7). Cooper and Mattson (10) have reported the most effective blockade of radiation emesis by a combination of promethazine, cimetidine, and thiethylperazine which are histamine H_1, histamine H_2, and dopamine receptor antagonists, respectively.

Since histamine- and dopamine-receptor antagonists are presumed to be relatively specific, the effectiveness of antagonists to these substances suggests their involvement in radioemesis. Histamine is known to be released by radiation (13) and has been proposed to be the substance responsible for the early transient incapacitation (ETI) following exposure to large doses of radiation (8). Our studies have shown, however, that injected histamine does not cause emesis even though it did cause the animals to be very unsteady and "sick." Furthermore, the time course of ETI and emesis do not correlate.

Our results with neurotensin-induced emesis show clear blockade by chlorpromazine, the presumably specific dopamine receptor antagonist. Although neurotensin and dopamine probably do not act at the same area-postrema receptor site, further single-unit experiments are needed to substantiate the claim. A much more likely explanation is that chlorpromazine is acting at a site subsequent to excitation of the area postrema. Chlorpromazine and most antihistamines are known to cross the blood-brain barrier. At the very least, the emetic pathway is a three-neuron circuit (area-postrema neuron to motor-emetic-center neuron to chest- and diaphragmatic-motor neurons). Drugs like the antihistamines and antidopaminergics, known to act against motion sickness, radioemesis, and most drug-induced vomiting (11, 19), might be expected to act thus if their action was not at the level of area postrema but rather at a synapse further down the pathway which was common to emesis induced by a variety of mechanisms.

It is for these reasons that we have studied domperidone, a dopamine-receptor antagonist reported not to cross the blood-brain barrier readily (15). Our results are somewhat equivocal in that there appeared to be an incomplete blockade of both neurotensin and angiotensin responses. The most charitable interpretation of these observations is that domperidone does not block area postrema receptors but does partially cross the blood-brain barrier. Further study is needed on this drug.

9

While the results of the single-unit recordings from the area postrema are very limited at present, we have progressed to a point where we will be able to determine what receptors exist on these neurons and what their pharmacologic sensitivities are.

On the basis of our results and the investigations reported in the literature, we hypothesize that emesis by radiation is induced by release of an active substance from some site. This substance travels through the blood to excite receptors on neurons of the area postrema, and no antagonist is known to block this excitation. The efferent neuron from the area postrema projects to the motor-emetic center where it synapses and releases a neurotransmitter which is probably either histamine or dopamine. The neurons from the motor-emetic center, possibly through more than one synapse, project to and excite thoracic and diaphragmatic neurons to produce emesis. The transmitters in these pathways may be either histamine or dopamine.

If this hypothesis is correct, we would predict the following:

1. Area-postrema neurons should have excitatory receptors for all emetic substances that do not cross the blood-brain barrier.

2. Receptors for emetic substances on area-postrema neurons should not be blocked by antidopamine or antihistamine drugs which are effective in blocking emesis.

3. The neurotransmitter contained in and released by area postrema efferent neurons is either dopamine or histamine, and the neurons in the motor-emetic center are excited by one of these amines.

4. Dopamine and histamine antagonists which do not cross the blood-brain barrier should be ineffective in blocking peptide-induced emesis.

5. Area-postrema neurons in the CTZ should show a great variety of excitatory receptors to emetic substances.

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